

I. Rejection under 35 U.S.C. §112, first paragraph, for lack of written description.

Claims 1-45 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the Application was filed, had possession of the claimed invention. Applicant has amended the claims to recite an endosomal lysing agent having one or more hydrolyzable functional moieties selected from the group consisting of ortho-esters, hydrazones, and cis-actonyls. Applicant submits that one of ordinary skill in the art reading the Specification would understand that the inventors had possession of the claimed invention. For example, support for hydrolyzable functional moieties such as ortho-esters, hydrazones, and cis-actonyls can be found on page 9, lines 10-18, and on page 10, lines 5-9. Given the support for these three types of hydrolyzable functional moieties as can be found in the originally filed Specification, Applicant requests that the rejection be removed.

II. Rejection under 35 U.S.C. §112, first paragraph, for lack of enablement. Claims 1-45 are rejected under 35 U.S.C. §112, first paragraph, on the ground that the Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant submits that the presently amended claims are enabled by the as filed Specification. Applicant has shown in the Examples starting on page 20 of the Specification that nucleic acids can be encapsulated in the claimed endosomal-lysing agents and can later be extracted from the lysing agents to recover the unharmed nucleic acids.

Examiner maintains that the Specification only provides enablement for endosomolytic lysing polymers composed of a poly(ortho-ester) having one or more tertiary amine group. Applicant submits that other hydrolyzable linkages such as hydrazones and actonyls are described in the application and would function as well as ortho-ester linkages in an endosomal lysing agent and that other ionizable groups such as carboxylic acids, primary amines, secondary amines, quaternary amines, sulfonium, phosphonium, phosphate, *etc.* could also be used. One of ordinary skill in the art would be aware of such ionizable groups since they are frequently used in organic molecules.

Applicant submits that the amended claims are enabled by the as-filed Specification and requests that the rejection be removed.

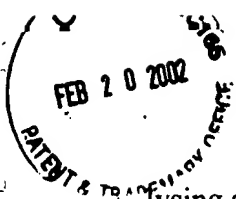
III. Rejection under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 42 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 has been amended to recite a “method for introducing a nucleic acid” rather than a “method for introducing a therapeutic agent” since the steps of the claim recite introducing a nucleic acid into a cell. Applicant respectfully submits that the claim is now definite and requests that the rejection be removed.

IV. Rejection under 35 U.S.C. §102(b), as being anticipated by Heller *et al.* Claims 1-15, 17-20, 22, 23, 26, 27, and 29-35 are rejected under 35 U.S.C. §102(b) as being anticipated by Heller *et al.* (*J. Controlled Release* 13:295-302, 1990), and claims 17-18 and 26-28 are rejected under 35 U.S.C. §103 as being unpatentable over Heller *et al.* Examiner states that Heller *et al.*

“teach a bioerodible linear polymeric vector comprising a pH-sensitive poly(ortho esters) that has been modified to incorporate tertiary amine groups and insulin, wherein the vector exhibits the insulin releasing activity in response to a decrease in pH at about 5 and 5.5.” Applicant submits that Heller *et al.* do not teach an endosomal lysing agent capable of effecting the lysis of an endosome in response to a change in pH, and therefore, Heller *et al.* cannot anticipate or render obvious the claimed invention.

Heller *et al.* teach a device for delivering insulin. The ortho-ester polymer used by Heller *et al.* degrades in response to a lower pH and thereby allows the insulin trapped by the polymer to be released. The claimed invention recites a compound capable of effecting the lysis of an endosome. Degradation of the endosomal lysing agent having functionalities such as ortho-esters, hydrazones, or cis-actonyls releases an endosomolytic compound such as ethanol to destabilize the membrane and effect lysis of the endosome (page 10, lines 5-9). The polymer disclosed by Heller *et al.* to deliver insulin does not teach or suggest such a feature. Since the Heller *et al.* do not teach or suggest such a limitation—“wherein said compound is capable of effecting the lysis of an endosome in response to a change in pH”—as recited in the claims of the present application, Heller *et al.* cannot anticipate or render obvious the claimed invention. Applicant, therefore, respectfully requests that the rejection be removed.

V. Rejection under 35 U.S.C. §102(e), as being anticipated by, or in the alternative, under 35 U.S.C. §103, as being unpatentable over Bischoff *et al.* Claims 1-12, 15-27, 29-35, and 39-45 are rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §103 as being obvious over Bischoff *et al.* (U.S. Patent 6,218,370). Examiner states the Bischoff *et al.* teach compounds which anticipate or render obvious the endosomal



lysing agents of the claimed invention. Upon careful evaluation of the '370 patent Applicant only finds *esters* and not *ortho-esters* in the compounds disclosed by Bischoff *et al.* An ortho-ester is defined as compounds that have three alkoxy groups attached to the same carbon, for example, ethyl orthoacetate, $\text{CH}_3\text{C}(\text{OC}_2\text{H}_5)_3$. Since the esters and ortho-esters are quite different functional groups, Applicant submits that the '370 patent does not anticipate or render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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